IRON AND LEARNING POTENTIAL IN CHILDHOOD*

BETSY LOZOFF, M.D.
Associate Professor of Pediatrics
Case Western Reserve University School of Medicine
Rainbow Babies and Childrens Hospital
Cleveland, Ohio

IRON DEFICIENCY ANEMIA, one of the most common nutritional disorders in the world, has a peak prevalence among infants, affecting an estimated 25% of all babies.[1,2] Approximately 20% of adult men and 35% of adult women in the world are also anemic, and more than half of the anemia is thought to be due to iron deficiency.[3] Since anemia is a late manifestation of iron deficiency, an even greater percentage of individuals of all ages show the biochemical changes of iron lack that precede the development of iron deficiency anemia.

Until recently it was often presumed that iron deficiency anemia had few deleterious effects unless severe enough to compromise cardiovascular function. However, evidence that iron deficiency has important behavioral effects has steadily accumulated during the past decade. The resulting picture of behavioral alterations due to iron deficiency reflects the convergence of two independent but complementary investigational approaches: studies of central nervous system biochemical changes, primarily in laboratory animals, and studies of behavior before and after iron treatment, primarily in young humans. To underscore both findings about which there is growing consensus and issues requiring further study, biochemical work related to behavior will be summarized briefly and recent studies directly assessing behavior will be considered, describing in most detail those involving children.

ALTERED NEUROTRANSMISSION IN IRON DEFICIENCY

Nonheme iron is unevenly distributed in the mammalian brain, with high levels in some areas, such as the extrapyramidal regions.[4,5] Since biochemical work has been conducted mostly with rats, it is noteworthy that the distribution of brain iron is similar in rats and humans.[5] Brain iron accumu-

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lates from gestation to early adulthood,[4] and brain iron levels are more seriously affected by iron deficiency in very young animals than in adults. For example, rats made iron deficient between gestation and 21 days of age did not normalize their brain iron content even after five to seven weeks of an iron-supplemented diet,[6,7] whereas rats made iron deficient approaching adulthood did so after only one to three weeks.[8] Rats who sustained early iron deficiency also have persisting behavioral and learning deficits.[9-14] Although these lasting changes have yet to be explained, it is possible that they relate to altered central nervous system neurotransmission. Thus far, alterations in iron deficient animals have been identified in the dopamine, serotonin, and GABA (gamma-aminobutyric acid) systems.

Dopamine. Dopamine, the major neurotransmitter of the iron-rich extrapyramidal system, has been extensively studied in laboratory animals and in human diseases, including schizophrenia, depression, Parkinson's disease, and Huntington's chorea.[15-17] Recent research establishing an important role of the basal ganglia in cognitive and affective regulation as well as motor behavior[18] indicates that iron-related changes in the extrapyramidal region might be expected to have major behavioral consequences. Evidence for dopamine alterations in iron deficiency comes primarily from a series of connected experiments by Youdim and associates (reviewed in references 19 and 20).

Despite finding no apparent effects of iron deficiency on brain tyrosine hydroxylase, central nervous system (CNS) monoamine oxidase, brain content or turnover of dopamine, or dopamine-stimulated adenylate cyclase activity in the rate caudate nucleus, which is coupled to the D_1 dopamine receptor, these investigators found that iron-deficient rats behaved like rats treated with drugs known to diminish dopaminergic activity. Specifically, iron-deficient rats, like those treated with dopamine receptor blocking agents (neuroleptics), showed reduced motor activity after receiving the centrally acting drugs apomorphine[20] and d-amphetamine, inhibition of d-amphetamine-induced hypothermia, an increase in sleeping time when given barbiturates, and increases in both the prolactin-binding sites in the liver and the prolactin level in the serum.[21] (Prolactin levels increase with diminished dopamine activity because dopamine is an important inhibitor of prolactin release by the pituitary.) Youdim and coworkers have now shown a significant and selective reduction in the density of one type of dopamine receptor (D_2) in the striatum in iron-deficient animals.[20] The levels of a specific protein with a molecular weight similar to that of the D_2 receptor are also reduced.[22] Important age-related effects have been noted as well; the decrease in number of D_2 receptors, the apomorphine response, and the low iron levels were not reversed with treatment in 10-day-old rats, but they were

reversed in older rats.[10] Taken together, these findings indicate that iron deficiency modifies central dopamine D_2 processes, some of which are related to behavioral responses, and that the young animal may be especially vulnerable to these effects.

Serotonin. Serotonin is usually thought to have an inhibitory influence on behavior and seems to play a key role in homeostasis, helping the organism to modulate excessive stimuli of a wide variety and make appropriate responses.[23] It has been proposed that lowered serotonin activity may increase vulnerability to major affective disorders, and, in fact, research suggests that changes in serotonin relate to changes in mood, sleep, circadian rhythms, neuroendocrine function, anxiety, ability to cope with stress, and motor activity.[24] Iron seems to have a regulatory role in serotonin storage in the brain. Iron enhances serotonin binding to a partially purified serotonin binding protein present in synaptic vesicles,[25] and iron deficiency has been shown to decrease *in vitro* serotonin uptake by rat brain synaptic vesicles.[26] After dietary iron supplementation, uptake and kinetic measures returned to normal, even though the brain nonheme iron content remained low. Decreased serotonin uptake, which would make more serotonin available in the synapse, appears to be an adaptive response to compensate for an overall decrease in serotonergic neurotransmission.[27] Such an overall decrease would be compatible with observations that iron deficient rats show a marked blunting of the hyperactivity usually observed after serotonin synthesis is increased by administration of either L-tryptophan, MAO inhibitors, or a direct acting serotonin agonist.[20] These findings demonstrate that iron deficiency lowers serotonin activity in the CNS, even though no alterations have been observed in brain tryptophan levels, tryptophan hydroxylase activity, or the rate of synthesis and turnover of serotonin.[19,20]

In addition to its functions in the dopamine and serotonin systems, iron seems to play a role in the utilization of GABA,[28-30] a major inhibitory neurotransmitter that is relatively poorly understood as yet, and the distribution of iron overlaps with encephalin and luteinizing hormone-releasing hormone as well as that of GABA.[5] Research on neurotransmitters is unfolding so rapidly that the next decade may bring evidence of still other changes induced by iron deficiency or iron excess and lead to further clarification of iron's role in the CNS.

Although the behavior changes in iron deficient humans, which are described in the next section, may be compatible with alterations in the dopamine and serotonin systems, linking specific biochemical changes in iron-deficient animals to specific behavioral alterations in iron-deficient humans is

fraught with hazard. Furthermore, altered behavior in iron deficiency may be due to changes in the periphery as well as in the central nervous system. The research related to motor movement will be briefly mentioned to illustrate this point (see recent comprehensive reviews of the systemic biochemical changes[31] and changes in activity[32,33] induced by iron deficiency). Skeletal muscle is severely affected by iron deficiency. Myoglobin, which serves an oxygen transport and storage function in muscle, is decreased, and the iron-containing electron transport enzymes of the mitochondria are depleted. These changes seem functionally important: impairments in the capacity of the iron-deficient animal or human for sustained exercise have been consistently observed.[34-44] Since changes in muscle function have been produced in isolated and perfused rat limb muscles,[45] it is clear that a peripheral effect is involved. Yet the changes in dopaminergic and serotonergic neurotransmission produced by iron deficiency are also associated with alterations in movement. The relative importance of central and peripheral mechanisms in accounting for diminished work capacity and altered acitivity patterns has still to be determined. This illustration may serve as a reminder that a narrow focus on central nervous system biochemistry may prematurely limit understanding of the mechanisms producing behavioral changes in iron deficiency.

HUMAN STUDIES

In animal studies it is possible to make certain that iron deficient animals differ from controls only in their dietary iron intake; adequate intake of other nutrients can be controlled, and genetic endowment and rearing conditions can be made the same. However, in human populations, nutritional disorders are not uniformly distributed—they are more likely to occur in the context of poverty, environmental deprivation, and disadvantaged social conditions, all of which may adversely affect behavior and development. Recent studies of the behavioral effects of iron deficiency have addressed these methodologic challenges by increasingly careful attention to the social environment and other factors that may be associated with iron deficiency.

Infancy. Since iron deficiency is most prevalent in the six- to 24-month-old period, which coincides with the latter part of the brain growth spurt and with the unfolding of fundamental mental and motor processes, it is not surprising that 12 recent studies have focused on the behavior and development of iron-deficient infants. These several studies have yielded a set of findings that has been reproducible in broad general outline, even though some of the specific results still await replication. Taken as a group, these studies have been designed not only to establish whether behavioral alterations are present

among iron-deficient infants, but also to address three further questions, to be considered in turn: What is the degree of iron deficiency at which infant behavior is altered? Does iron therapy produce rapid changes in behavior? Does iron therapy completely correct these behavioral alterations?

Degree of iron deficiency affecting behavior. The first question has been studied because iron deficiency occurs along a physiologic continuum. Reductions in total body iron have been grouped into three stages of progressively increasing severity, based on current understanding of iron metabolism and defined by appropriate laboratory criteria.[1] Serum ferritin concentration, transferrin saturation, free erythrocyte protoporphyrin, and mean corpuscular volume are the tests most widely used in addition to hemoglobin or hematocrit. The terms "iron replete" or "iron sufficient" have been used to denote a normal total body iron content. The term "iron depletion" has been used to designate a decrease in body storage iron without any effect on hemoglobin iron or iron in other functional iron compounds. This stage of iron deficiency is usually reflected by a decrease in the serum ferritin concentration without changes in other measures of iron status. The terms "iron restricted erythropoiesis" or "iron deficiency without anemia" are used to describe an additional decrease in the iron supply such that heme production is limited, even though the resulting depression in the hemoglobin concentration or hematocrit is too slight to be detected using reference limits derived from population studies. In addition to a low serum ferritin, transport iron is decreased with a reduction in the serum transferrin saturation. Because insufficient iron is available to combine with protoporphyrin to form heme, protoporphyrin accumulates in the red cells and the free erythrocyte protoporphyrin increases. "Iron deficiency anemia" designates the anemia resulting from a further diminution in total body iron. The hemoglobin concentration is below reference limits, the serum ferritin and transferrin saturation decreased and the free erythrocyte protoporphyrin elevated. The mean corpuscular volume decreases at about the same time the anemia becomes manifest.

At what point in the continuum of iron deficiency is infant behavior adversely affected? A recent study by Lozoff et al. in conjunction with the Hospital National de Ninos in Costa Rica[46] addressed this issue by enrolling in a single study a relatively large number of otherwise healthy infants with varied iron status. The sample consisted of 191 12- to 23-month-old infants divided into groups ranging from most to least iron deficient as follows: iron deficient anemic (n = 52), intermediate in hemoglobin level and iron deficient (n = 45), nonanemic iron deficient (n = 21), nonanemic iron depleted (n = 38),

and nonanemic iron sufficient (n = 35). The data of the 52 anemic infants were further analyzed with respect to severity of anemia (moderate – Hb ≤ 10.0 g/dl, n = 34; mild – Hb 10.1 – 10.5 g/dl, n = 18). The Bayley Scales of Infant Development[47] were administered before and after one week and after three months of i.m. or oral iron with appropriate placebo controls. The children were all born at term, were free of medical problems, had normal physical examinations, and low lead levels (mean lead = 10.8 μg/dl), and had no evidence of growth failure or deficiencies in B_{12}, folic acid, or protein. Iron deficiency anemia seemed due to dietary factors in this sample, since fewer of the anemic infants had been breast fed, they were weaned at an earlier age, and they consumed more cow's milk than the other infants.

Infants with moderate iron deficiency anemia (Hb ≤ 10.0 g/dl) were found to have lower mental and motor test scores than appropriate controls, and infants with mild anemia (Hb 10.1–10.5 g/dl) received lower motor scores but not mental scores. The mean mental test score of the moderately anemic infants was eight points below that of infants with higher Hb levels, and the mean motor score of the entire anemic group was 10 points below that of infants with Hb > 10.5 g/dl. Infants with iron depletion or iron deficiency with intermediate or normal Hb levels did not receive lower mental or motor developmental test scores.

The results of the Costa Rican project are noteworthy for several reasons. The study was community based, thus minimizing biases potentially involved in research with patient populations. Infants with all known risk factors for altered hematologic or developmental status had been carefully excluded. Iron-deficient and iron-depleted conditions were confirmed by hematologic response to iron therapy. Finally, an extensive set of background variables relating to birth, general nutritional status, lead level, family background, home environment, and parental I.Q. failed to reveal any factor other than iron deficiency anemia that might explain the findings.

Similar results were obtained in another study with a strong research design, recently completed by Walter and associates in Chile.[48] This project is exceptional, because the infants were studied prospectively from early infancy as part of a field trial of iron-fortified foods in which infants in an entire community were randomly assigned iron fortification or control. This feature of the study is especially important, since the disadvantages in the home environment that might be associated with iron deficiency were largely controlled by the random allocation procedure. Iron measures were obtained at nine and 12 months and developmental assessments initially performed at 12 months. Not surprisingly, most of the iron deficiency and anemia occurred

among the infants who did not receive iron-fortified foods. As in the Costa Rican study, iron status was ultimately confirmed by hematologic response to therapeutic iron, administered after 12 months of age, and the Bayley Scales of Infant Development were used to give an overview of the infants' current functioning. The developmental assessments at 12 months indicated that the 39 infants with iron deficiency anemia had significantly lower mental and motor scores than either 127 iron-deficient nonanemic infants or 30 iron-replete controls. The differences were similar to those obtained in Costa Rica: mental scores of the anemic infants averaged six–seven points lower than those of nonanemic infants, motor scores averaged nine–11 points lower, and lower test scores were not observed in the absence of iron deficiency anemia.

Due to its prospective design, the new study by Walter et al.[48] provides insight into the importance of chronicity and severity in iron deficiency anemia. Those infants who were anemic at both nine and 12 months had significantly lower developmental test scores than those with anemia of less than three months duration (i.e., those who had normal Hb levels at nine months and anemic levels at 12 months). As would be expected by the pathophysiology of iron deficiency, infants who were anemic at both nine and 12 months of age had lower Hb levels than those whose anemia was not apparent until the 12-month testing. Although results of other studies have suggested a need for considering the chronicity, severity, and timing of iron deficiency, the results of this project, unique among published studies on the behavioral effects of iron deficiency for its design as a preventive trial, confirm the importance of such factors.

The results of research published to date support the conclusions of the studies in Chile and Costa Rica that iron deficiency severe enough to cause anemia is associated with impaired performance on developmental tests in infancy. In sum, all five published studies with careful definition of iron status and nonanemic control groups, conducted in Guatemala,[49] Chile,[48,50] United Kingdom,[51] and Costa Rica[46] found clinically and statistically significant lower mental test scores among anemic infants prior to treatment. Lower motor test scores among anemic infants were also noted in four of the five studies.[46,48,49,51] The alterations in motor test performance are particularly interesting in view of the changes in motor activity in iron-deficient laboratory animals and the interrelatedness of locomotor function and cognitive development in human infants. Although consistent, these results do not mean that the observed alterations are due to anemia per se rather than to iron deficiency, since iron-deficiency anemia develops only after a relatively prolonged period of iron lack. Significant cognitive or motor deficits have not yet

been found among nonanemic infants with varying degrees of iron lack, but the limited number of studies makes it premature to conclude that there are no ill effects.

That lower mental and motor test scores have been observed among iron-deficient anemic infants raises the further questions of why their scores were lower and how they might improve rapidly. Recent investigations have often assumed that disturbances in affect, arousal, or attentiveness were important determinants of anemic infants' poorer developmental test performance, and, in fact, seven of eight studies noted behavioral differences between iron deficient and control infants during developmental testing or play or behavioral changes after treatment.[48,50,52-58] Such behavioral alterations include solemnity, fearfulness, irritability, lack of persistence, short attention span, tiredness, tension, hesitation or withdrawal from the examiner, and increased contact with the mother. Moreover, these disturbances seem closely related to poor developmental test performance. In our previous study in Guatemala anemic infants who were unduly fearful, unhappy, tired, tense, and hesitant or withdrawn with the examiner received low mental test scores, whereas anemic infants who were rated normal in affect achieved mental test scores comparable to those of nonanemic controls and normal by U.S. standards.[55,59] Walter et al.[48] recently found a similar pattern: lower mental scores were noted among anemic infants who were abnormal in affect or task orientation.

Rapid changes with iron treatment. Until the last two or three years, most studies examining the behavioral effects of iron deficiency were designed to detect changes in developmental test performance within five to 11 days of starting iron therapy. This emphasis on short-term treatment effects was guided by two considerations: a) clinicians, in describing iron deficient anemic babies as irritable, apathetic, and distractible, have commented that these characteristics seem to disappear within a few days of iron treatment,[33] and b) early retesting might allow any behavioral changes to be attributed to brain rather than blood, i.e., to altered central nervous system function rather than to the correction of anemia.

Consistent results have been obtained in all five studies that included a placebo treatment—the investigations in Guatemala[49] and Costa Rica,[46] Oski and Honig's original study,[52] Moffatt et al.'s project in Canada (personal communication), and Walter et al.'s second study.[48] Together, these studies indicate that short-term increases in test scores observed among iron-treated anemic infants are not significantly greater than those among placebo-treated anemic infants; increases in scores were observed regardless of the treatment

the infants received or their iron status prior to treatment. The results of these studies confirm that an increase in Bayley test scores can be expected if the Bayley Scales are readministered after a short time period and that these improvements probably indicate the effect of practice since they cannot be attributed to iron therapy.

Complete correction with iron therapy. The early search for rapid behavioral changes was motivated by an interest in attributing improvements in behavior and in test scores to improved function of iron-dependent central nervous system enzymes rather than to the correction of anemia. Although separating the effects of iron deficiency from those of anemia is important, a more pertinent question from a clinical perspective is whether or not iron therapy completely corrects any behavioral abnormalities, regardless of how soon changes might be detectable. Until very recently none of the infant studies could address this issue, because none included assessments after a course of iron therapy.

Our recent study in Costa Rica[46] was specifically designed to examine the effects of a course of treatment commonly used in practice—three months of oral iron therapy. All infants responded to treatment by becoming nonanemic, but, as would be expected, some of them still showed biochemical evidence of iron deficiency, especially high FEP or low ferritin levels. On the basis of hematologic response to iron therapy, infants who became iron sufficient by study conclusion were distinguished from those who did not correct all evidence of iron deficiency. Most of the group that was initially moderately anemic did not become completely iron sufficient after three months and concluded the study with mental scores that were still significantly lower (mean = 93.2) than those of infants with initial Hb levels >10.0 g/dl, regardless of whether the latter were iron sufficient after three months (mean = 101.8) or not (mean = 100.2). Three months of iron therapy was sufficient to correct completely the iron deficiency of only nine moderately anemic infants (26%). Lower mental test scores were no longer evident among these infants. However, the absence of a post-treatment difference was due not to significant improvements in the mental test scores of the formerly moderately anemic infants but to the slight but statistically significant decline in mental scores after three months in the comparison group. Such a decline in test scores during the latter part of infancy has been reported in a variety of other disadvantaged populations, perhaps because language development plays a bigger role in infants' tests in the second year of life. In contrast to the pattern of mental test score results, the 18 previously mildly or moderately anemic infants who became iron sufficient by study's end did

show a substantial increase in motor test scores, averaging 10 points, while the motor scores of infants with Hb levels >10.5 g/dl who became iron sufficient remained approximately the same. Previously mildly or moderately anemic infants who did not become iron sufficient concluded the study with motor scores (mean = 106.3) that were still substantially lower than those of infants with initial Hb levels >10.5 g/dl (mean = 114.9). There was laboratory evidence that anemic infants who did not become iron sufficient after three months had more severe and chronic iron deficiency.

Though the improvement in motor scores was substantial and indicates a beneficial effect of treatment, a worrisome result is that most anemic infants did not show improvements with iron therapy. Lack of improvement after iron therapy has also been the primary finding in two other studies, one in the United Kingdom[60] and the other in Chile.[48] (The study by Moffatt et al. (personal communication, 1987), despite follow-up after two months, does not address this issue, since all anemic children were treated with iron and there was no nonanemic control group.) Aukett et al.[60] in a double blind randomized study of 17- to 19-month-old iron-deficient children in the United Kingdom found that even among those who showed a distinct hematologic response to two months of therapeutic iron (Hb increase >2 g/dl), most (58%) failed to show the rate of development expected for their age. The expected rate of development was defined as the number of new items on a developmental screening test that 50% of average children in this age group would be expected to pass over a two-month interval. It is important to note, however, that a greater proportion of children showing such a marked hematologic response to iron therapy did achieve the expected rate of development than those who were treated with iron but whose increase in Hb level was less than 2 g/dl. The use of placebo treatment for two months is a methodologically strong, though controversial, aspect of this study's design, but the results are difficult to compare to those of other studies for several reasons: the developmental measure was unlike that used in other projects; analyses of mean developmental scores revealed no significant effects of treatment; and the decision to consider an increase in Hb of 2 g/dl or more as indicating effective treatment has no counterpart in other studies and may be a somewhat arbitrary cut-off that separated the children in this particular study. Nonetheless, this study, in conjunction with the one in Costa Rica,[46] suggests that iron therapy may favorably affect developmental test scores among some anemic infants, but not the majority. The only other study relevant to the question of longer-term iron therapy is the second study by Walter and associates in Chile,[48] which is directly comparable in design to that in Costa

Rica. As in the latter study, the administration of oral iron was carefully supervised and an excellent hematologic response documented. However, in contrast to the results obtained in Costa Rica and the United Kingdom, even those anemic infants who corrected their hematologic status failed to improve their scores. Thus, no improvements in mental or motor test scores were observed after three months of treatment.

Inasmuch as the follow-up period in the Costa Rican, Chilean, and British studies was only two or three months, these studies cannot determine whether ill effects of iron deficiency anemia persist beyond infancy. The lower mental and motor test scores among many of the iron-deficient anemic infants might have responded to a more extended course of iron therapy. A study of such a treatment course is nearing completion in Costa Rica. It is also possible that the deficits might persist even if laboratory evidence of iron deficiency had been entirely corrected in all the anemic infants. This outcome would indicate that iron-deficiency anemia in infancy, perhaps of a particular severity or chronicity, has irreversible ill effects. Alternatively, these differences might disappear spontaneously, especially because Bayley scores in the second year of life are only moderately correlated with measures of cognitive function in childhood.

To determine if there are lasting developmental effects of iron deficiency anemia in infancy, the children in our study in Costa Rica and Walter's study in Chile are being reassessed at five and five and a half years, respectively. Preliminary results from both samples indicate that the formerly anemic children are still testing lower in mental and motor functions. Based on data of 81% of the original Costa Rica sample,[61] the 28 children who had been moderately anemic (Hb$\leq$10.0 g/dl), despite having had their anemia corrected in infancy, tested significantly lower than the rest of the children on the following measures: WPPSI I.Q. (most markedly in Performance IQ), the Woodcock-Johnson Preschool Scale (especially Quantitative Concepts and Visual Matching), and the Bruininks-Oseretsky motor test (most markedly in Gross Motor score). All these differences remained statistically significant after controlling for maternal I.Q. and regardless of whether or not iron therapy in infancy had resulted in complete correction of iron deficiency as well as anemia. Walter is also finding lower scores among the formerly anemic group from the Chilean sample (personal communication).

Two other studies of infants support the possibility that iron deficiency anemia in infancy may have lasting ill-effects. In an abstract, Cantwell[62] described a preventive trial of iron therapy in which subjects were followed for six to seven years. Children who had been anemic between six and 18

months of age (n = 32) were less adept than children in whom anemia had been prevented (n = 29) at balancing on one foot, tandem walking, and repetitive hand or foot movements. The I.Q. scores of the formerly anemic children were also six points lower. In a follow-up study of Israeli children treated with iron for anemia in infancy, Palti et al.[63] noted that lower hemoglobin levels at nine months were associated with lower developmental and I.Q. test scores obtained as many as four years later. Even after controlling for other important factors, such as mother's education, social class, and birth weight, these investigators found a 1.75-point increase in I.Q. at age five with each 1 gm/dl increment in hemoglobin level. Upon reevaluation in second grade, the formerly anemic children were rated by teachers as being significantly lower in learning achievement and lower in positive task orientation than controls.[64] These effects on I.Q. and learning achievement scores are noteworthy because the infants' anemia had been diagnosed early and treated with iron as part of a health surveillance program. Although iron status was documented only by hemoglobin levels and hematologic response to iron treatment was not confirmed, the results suggest that anemia, as commonly diagnosed and treated in many parts of the world, may affect intellectual development even several years after it has been treated.

The lack of improvement with iron therapy in the studies during infancy and these follow-up results make it difficult to be certain that the lower scores are due to iron deficiency anemia rather than some other nutrient or environmental deprivation. Although we and other investigators have seriously grappled with this possibility by exhaustive attempts to measure and control potentially intervening factors, the possibility that iron deficiency anemia is acting as a marker for other underlying problems must be kept in mind. Nonetheless, the results indicate that iron deficiency, or some closely associated but as yet unidentified factor, places children at risk for lasting developmental disability.

Age periods after infancy. Studies of behavioral changes in age periods after infancy are heterogeneous in terms of methodology and of the age groups examined. Although this diversity means that few results have yet been replicated, these studies have addressed two important questions that are methodologically difficult to study in infancy: what are the specific cognitive functions that may be impaired by iron deficiency and what is the functional significance of behavioral alterations due to lack of iron?

Studies of preschool-aged children in the U.S., Guatemala, and Java have detected changes in attentional processes and in oddity and discrimination learning.[65,66,67] These changes seemed to improve with iron therapy. Re-

searchers in India also noted that iron-treated anemic school boys showed substantial improvements on a battery of cognitive function tests, including visual recall (a test of memorizing capacity), digit span (a test of attention, short-term auditory memory, and auditory sequencing), mazes (a test of discrimination and perception) and a clerical task (a test of discrimination and perception).[68] Studies of school-aged children in Indonesia and Thailand point to significant functional impairments (lower achievement test scores) that improved with treatment in one study[69] but not in a large, carefully-designed and executed study that attempted to replicate the findings.[70] The results of these studies, when taken together, suggest that behavior changes in older children, in contrast to those in infants, may improve with iron therapy. Research on the effects of iron deficiency on cognitive function and affect in adolescence and adulthood is too limited and flawed at the present time to support any conclusions.[19]

SUMMARY

Cognitive function. There is reasonably good evidence that mental and motor developmental test scores are lower among infants with iron deficiency anemia. Although the research on cognitive function in iron deficient older children and adults is sparse and diverse, it suggests that there may be alterations in attentional processes associated with iron deficiency. Iron therapy has not yet been shown effective in completely correcting many of the observed disturbances. Although some aspects of cognitive function seem to change with iron therapy, lower developmental. I.Q., and achievement test scores have still been noted after treatment. The behavioral effects of iron-deficiency anemia may be due to changes in neurotransmission. However, the biochemical bases are not yet completely understood.

Noncognitive disturbances. A variety of noncognitive alterations during infant developmental testing has also been observed, including failure to respond to test stimuli, short attention span, unhappiness, increased fearfulness, withdrawal from the examiner, and increased body tension. Exploratory analyses suggest that such behavioral abnormalities may account for poor developmental test performance in infants with iron deficiency anemia. These studies indicate the fruitfulness of examining noncognitive aspects of behavior such as affect, attention, and activity, in addition to specific cognitive processes.

Activity and work capacity: There has been a steady accumulation of evidence that iron-deficiency anemia limits maximal physical performance, submaximal endurance, and spontaneous activity in the adult, resulting in

diminished work productivity with attendant economic losses. The relative importance of central and peripheral mechanisms underlying these effects, the extent to which anemia or iron deficiency separate from anemia is responsible, and the counterpart in infants and children remain to be established.

This essay has examined recent evidence from research on central nervous system biochemistry and from human studies that iron deficiency adversely affects behavior by impairing cognitive function, producing noncognitive disturbances, and limiting activity and work capacity. The body of research taken as a whole provides increasingly persuasive arguments for intensifying efforts to prevent and treat iron deficiency anemia.

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